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10/500,933	09/14/2005	Shangguan Tong	TRA-027.01	1561

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,933	TONG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69,71-142 and 144-168* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-69,71-142 and 144-168* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/8/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 6/25/07.

Applicant's election with traverse of group 1 claims 74-141 and 144-146 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 70 and 143 were canceled.

Claims 1-69, 71-142, and 144-168 remain pending and are under consideration.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specifically, the name and citizenship of Shangguan Tong were altered, but the alterations were not initialed or dated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-69, 71-86, 88-142, and 144-168 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12, 14-69, 71-86, 88-142, and 144-168 are indefinite because the metes and bounds of "aqueous medium Z1" are unclear. In particular it is unclear how "Z1" is intended to further limit the term "aqueous medium". The specification fails to provide any limiting definition of Z1 that would allow one of skill in the art to determine the metes and bounds of the claim.

Claim 26 is indefinite in its recitation of "wherein the RNA is... RNA interference". RNA interference is a phenomenon, not an RNA.

Claims 82 is indefinite in its recitation of "C,-C3 alcohol". This phrase has been interpreted as "C_1-C_3 alcohol".

Claim 145 requires an aqueous buffer but simultaneously disallows any hydrating agent. However, an aqueous buffer is a hydrating agent, so the claim is indefinite.

Claim 130 is indefinite in its recitation of "up to about 1 of the weight of the gel". Insertion of '%' immediately after '1' is suggested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 152 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention and Breadth of the Claims

Claim 152 is directed to a method of transfecting a cell in a human in need of gene therapy. The nucleic acid used to transfect the cell is a plasmid DNA encoding a gene necessary for the gene therapy. The scope of diseases or disorders to be treated by gene therapy is not limited, so the method embraces treatment of any disease or disorder by gene therapy. However, no specific disease or disorder is set forth in the claims or specification, and no specific gene is suggested for the therapy of any disease or disorder. Similarly, no treatment regimen for any disease is set forth, i.e. no dosages, course of administration, or guidelines for responding to changes in patient status are disclosed. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the disclosure of diseases, therapeutic genes, and appropriate administration protocols cannot be considered minor details which can be omitted in the

process of providing an enabling disclosure, particularly in view of the state of the art at the time of the invention.

State of the Art

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Verma et al (Nature 389: 239-242, 1997) taught that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors stated further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirmed the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Rosenberg et al (Science 287 :1751, 2000) stated that "[a}t present

the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials." See first full paragraph. Juengst (BMJ 326: 1410, 2003) indicated that the effects of gene therapy on cells are often multiple and unpredictable. See title and last sentence of first full paragraph of column 2. In summary, it is clear that gene therapy is considered highly experimental area of research at this time, and researchers acknowledge that demonstrable progress to date has fallen short of initial expectations due to inadequate delivery and expression systems, and the unpredictable and pleiotropic effects of gene insertion and/or expression.

Guidance and Examples in the Specification

The instant specification is directed to the issue of gene delivery, but does not disclose any evidence that the art-recognized difficulties with gene delivery or expression have been overcome by the claimed invention. No working example of gene therapy is presented.

Amount of Experimentation Required

Because the specification provides no guidance or working examples as to how to overcome the art-recognized barriers to the practice of gene therapy, particularly in view of the breadth of diseases and subject organisms encompassed by the claims, and

because the specification omits elements which are critical to the claimed methods, one of skill in the art could not practice the invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-34, 38-69, 71-73, and 147-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Eppstein et al (US Patent 4897355) as evidenced by GenBank Accession No. M77788.

Claims 1-27, 29-34, 38-69, 71-73, and 152-168 are directed to liposomes comprising nucleic acids. The liposomes are made by a particular process which has been given no patentable weight in the determination as to whether the claimed products are novel. Eppstein taught a variety of liposomes comprising nucleic acids. The liposomes comprise varying amounts of the fusogenic lipid dioleoylphosphatidylethanolamine (DOPE) or dioleoylphosphatidylcholine (DOPC) (see column 16, lines 13-27) . The nucleic acid may be plasmid DNA (e.g. plasmid pSV2CAT), an antisense RNA oligonucleotide, or dsRNA of a length of about 130 bp (see column 3, lines 56-59; column 8, lines 32-40 and 43-45; column 10, lines 56-59; column 48 lines 24-50, and paragraph bridging columns 48 and 49). Pertinent to the plasmid size limitations of claims 18-24, GenBank Accession No. M77788 shows that

pSV2CAT is 5003 base pairs in length. The liposomes may comprise a variety of lipids including distearoyl phosphatidylcholine and cholesterol (see column 16, lines 53-and 54; and column 38, line 37). Eppstein also taught methods of transfecting eukaryotic cells in vitro at 37°C (column 45, lines 43-52), as well as intravenous delivery to humans (see column 8, lines 1-13; column 10, lines 37-62; column 12, lines 48-53; column 13, lines 27-29; and column 20, lines 21-41).

Thus Eppstein anticipates the claims.

Claims 1-16, 25, 29-31, 33, 34, 38-69, 71-80, 87, 88, 90, 99, 102-104, 106, 107, 123, 141, 142, 144, 147, and 153-168 are rejected under 35 U.S.C. 102(b) as being anticipated by Papahadjopolous et al (US Patent 4,235,871), as evidenced by Harvie et al (US 20050025821).

Claims 1-16, 25, 29-34, 38-69, 71-80, and 153-168 are directed to liposomes comprising nucleic acids. The liposomes are made by a particular process which has been given no patentable weight in the determination as to whether the claimed products are novel. Papahadjopolous taught a variety of liposomes comprising nucleic acids such as DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68 column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine (PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. Harvie provides evidence that PS is a fusogenic lipid at paragraph 261.

Papahadjopolous taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30. The inert solvent is any solvent that can be substantially removed from the lipid when desired such as esters, ethers, alcohols, and/or ketones. See column 4, lines 45-52. Aqueous medium may be added in a first small increment, followed later by addition of further aqueous medium. See column 6, lines 5-13. The gel is washed in an aqueous medium and unincorporated aqueous material is removed by centrifugation, dialysis, or column chromatography. See column 6, lines 22-26.

Papahadjopolous also envisions methods of transferring genetic information to eukaryotic cells. See column 9, lines 31-36

Thus Papahadjopolous anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74, 89, 111-140, and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous et al (US Patent 4,235,871).

Papahadjopolous taught a variety of liposomes comprising nucleic acids such as

DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68 column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine (PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. Harvie provides evidence that PS is a fusogenic lipid at paragraph 261.

Papahadjopolous taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30.

Regarding claim 89, Papahadjopolous taught addition of an aqueous solvent to the gel, rather than addition of the gel to an aqueous solvent, but this detail is considered to be a simple matter of design choice, and is therefore an obvious variant of the method of Papahadjopolous.

Regarding claims 111-122 and 146, Papahadjopolous is silent as to the total amount of lipid forming and fusogenic lipid expressed as a weight-percent of the gel, but the amounts of these lipids are considered to be result-effective variables that are obvious to optimize in order to modulate the characteristics of the resultant liposomes. See e.g. column 4, lines 53-58; and column 6, lines 11-18 and 28-34.

Regarding claims 124-135, Papahadjopolous is silent as to the ratio of the weight of the increment of aqueous medium that can be used to wash the gel, and the weight

of the gel itself. However, this is a parameter that would be routinely optimized by one of ordinary skill, see e.g. column 4, lines 53-58.

Regarding claims 136-140, Papahadjopolous is silent as to the total amount of nucleic acid expressed as a weight-percent of the gel, but the amounts of the nucleic acid is clearly a result-effective variable that is routinely optimized by one of ordinary skill. in order to modulate the characteristics of the resultant liposomes. See e.g. column 6, lines 11-18 and 28-34.

Regarding claim 146, Papahadjopolous is silent as to the total amount of organic solvent remaining in the gel, but it is clear that this is a result-effective variable that is routinely optimized by one of ordinary skill. See e.g. column 4, lines 53-58

Claims 1, 17-24, 26-28, 33, 91-98, 100, 101 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous et al (US Patent 4,235,871) in view of Eppstein et al (US Patent 4897355) taken with the evidence of GenBank Accession No. M77788.

The teachings of Papahadjopolous are summarized above and render obvious methods of making liposomes comprising nucleic acids.

Papahadjopolous did not specifically teach plasmid DNA or oligonucleotides.

Eppstein taught that liposomes could be used to encapsulate and deliver to cells plasmid DNAs and oligonucleotides, including pSVCAT (5 kbp) and oligonucleotides of an average length of about 130 bp. See column 3, lines 56-59; column 8, lines 32-40 and 43-45; column 10, lines 56-59; column 48 lines 24-50, and paragraph bridging

columns 48 and 49. GenBank Accession No. M77788 provides evidence that PSVCAT is 5003 base pairs in length. Eppstein also taught a variety of lipids that could be used to form liposomes including dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine, and cholesterol (see paragraph bridging columns 7 and 8; column 16, lines 53-and 54; and column 38, line 37).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Papahadjopolous to encapsulate the plasmid or oligonucleotides of Eppstein because Papahadjopolous suggests that the liposomes will protect nucleic acids from degradation (see e.g. column 13, lines 59-67), and because one of ordinary skill would clearly appreciate their utility for this purpose in view of the teachings of Eppstein. It would have been similarly obvious to use the lipids of Eppstein in the methods of Papahadjopolous, because MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. In this case the lipids of Eppstein are clearly suitable for making liposomes.

Claims 1, 35-37, 74, and 108-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous et al (US Patent 4,235,871) in view of Meers et al (US Patent 6,120,797).

Papahadjopolous taught a variety of liposomes comprising nucleic acids such as DNA or RNA. See column 3, lines 28-40; column 6, lines 31-43; column 8, lines 45-68

column 13, lines 59-67; and claims 16 and 17. The liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidylserine (PS), and may also comprise a variety of other lipids including cholesterol, see paragraph bridging columns 3 and 4. Harvie provides evidence that PS is a fusogenic lipid at paragraph 261.

Papahadjopolous taught a method of making liposomes by combining lipids as discussed above and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium. See entire document, especially e.g. claim 1, and column 4, line 45 to column 6, line 30.

Papáhadjopolous did not teach N-acyl phosphatidylethanolamines.

Meers taught N-acyl phosphatidylethanolamines, including a N-dodecanoyl dioleoyl phosphatidylethanolamine, for use in liposome formation. See e.g. abstract; and column 4, lines 40-51.

It would have been obvious to use the lipids of Meers in the liposomes of Papahadjopolous because Meers taught that it promotes membrane fusion. See e.g. column 1, lines 48-60.

Claims 81-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopolous et al (US Patent 4,235,871) as applied to claims 74, 111-140, and 146 above, and further in view of Lenk et al (US Patent 5,169,637).

The teachings of Papahadjopolous are summarized above and render obvious

methods of making liposomes by mixing liposome forming and fusogenic lipids in any solvent that can be substantially removed from the lipids when desired, such as esters, ethers, alcohols, and/or ketones. See column 4, lines 45-52.

Papahadjopolous did not specifically teach acetone, ethanol, methanol, or 2-propanol.

Lenk taught a variety of solvents that cold be used to solubilize lipids, including acetone, ethanol, methanol, or 2-propanol. See table VI at column 40.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any solvent that could be substantially removed from the lipids when desired, such as alcohols or ketones, because Papahadjopolous specifically suggested this. It would have been obvious to use acetone, ethanol, methanol, or 2-propanol because these are clearly volatile organic solvents that can be used to solubilize lipids in view2 of the teachings of Lenk. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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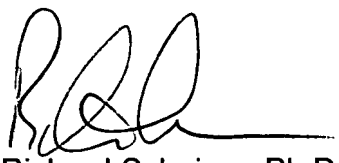

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